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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,734	10/01/2003	Kevin H. Gardner	UTSD:1510-1	4912
23379 7590 01/05/2007 RICHARD ARON OSMAN SCIENCE AND TECHNOLOGY LAW GROUP 242 AVE VISTA DEL OCEANO SAN CLEMENTE, CA 92672			EXAMINER SWOPE, SHERIDAN	
			ART UNIT	PAPER NUMBER

1652

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/677,734

Applicant(s)

GARDNER ET AL.

Examiner

Sheridan L. Swope

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21 and 22 is/are pending in the application.
- 4a) Of the above claim(s) 22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

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DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1652.

Applicant's response of October 9, 2006, to the action mailed September 1, 2006, is acknowledged. It is acknowledged that Claim 21 has been amended and that no claims have been added or deleted. Claims 21 and 22 are pending. Claim 22 was previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claim 21 is hereby reexamined.

Abstract

Objection to the Abstract filed October 13, 2005 is maintained because, as amended, the Abstract is a single, run-on phrase that is not a sentence.

Specification-Objections

Objection to the specification for having two versions of the figure legends, as acknowledged by Applicants in their response, is maintained.

The specification is objected to for, on page 18 line 7, "Compound KG0721, as well as X others...". It is unclear what "X" refers to.

The specification is objected to for having an undefined abbreviation, Dd.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Provisional rejection of Claim 21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of US Application 10/677,733, for the reasons set forth in the prior action, is maintained. Applicants state they will file a terminal disclaimer when the instant invention becomes allowable.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of Claim 21 under 35 U.S.C. 112, second paragraph, as being indefinite for the reasons set forth in the prior action, is withdrawn. Applicants, in their response, have affirmed that Claim 21, in reciting a method of "changing a functional surface binding specificity of a selected PAS domain...comprising the steps of: introducing into the hydrophobic core of the PAS domain a foreign ligand...", encompasses both a method to (i) screen for ligands that, via binding to the hydrophobic core, alter PAS domain structure and (ii) alter PAS domain structure by contacting the domain with a ligand that is known alter the PAS domain structure by binding to its hydrophobic core.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claim 21 under 35 U.S.C. 112, first paragraph lack of enablement, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A.) As explained in the specification, suitable foreign ligands may be screened from libraries of synthetic and natural compounds. Such screening was exemplified with HIF2a PAS B, wherein a “lead” ligand was identified (pg 13, 18, and 31; Fig 1).

(B.) The practitioner does not require any a priori structural characteristics of the recited “foreign ligand” to practice the method.

(C.) Introducing the foreign ligand into the hydrophobic core of the PAS domain can be effected by simply mixing a PAS domain-containing protein with the ligand in solution (pg 20).

These arguments are not found, or found, to be persuasive for the following reasons.

(A) Reply: It is acknowledged that the specification teaches screening 772 compounds for binding to the PAS domain of HIF2a using 1H/15N-HSQC NMR, identifying 21 compounds that bind, and, using the minimum chemical shift method of Farmer et al, 1996, determining which residues of the PAS domain a specific compounds bind (pg 18; Fig 3). However, said example does not disclose whether any said 21 compounds bind to a hydrophobic

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core of the PAS domain. Furthermore, said example does not disclose whether binding of any of said 21 compounds affects any functional surface binding specificity, as recited in Claim 21.

Moreover, screening the unlimited number of naturally-occurring and synthetic compounds for binding to the extremely large number of HIF2a PAS domains, wherein the HIF2a PAS domain has any structure, and further determining whether a surface binding specificity is altered clearly represents undue experimentation. The specification fails to teach the skilled artisan how to make and use the full scope of the invention.

(B) Reply: It is acknowledged that *a priori* structural characteristics of the recited foreign ligand are not required to practice the method.

(C) Reply: This argument is found to be persuasive.

Written Description

Rejection of Claim 21 under 35 U.S.C. 112, first paragraph written description, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(D.) As explained in the specification, suitable foreign ligands may be screened from libraries of synthetic and natural compounds. Such screening was exemplified with HIF2a PAS B, wherein a “lead” ligand was identified (pg 13, 18, and 31; Fig 1).

(E.) The practitioner does not require any *a priori* structural characteristics of the recited “foreign ligand” to practice the method.

These arguments are not found or found to be persuasive for the following reasons.

(D) Reply: As explained above, the example on page 18 does not disclose whether any of the identified binding 21 compounds bind to a hydrophobic core of the PAS domain or

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whether binding of any of said 21 compounds affects any functional surface binding specificity.

Therefore, the skilled artisan cannot conclude that Applicants were in possession of the claimed invention.

(E) Reply: See (B) above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of Claim 21 under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(F.) HIF1 α is structurally and functionally distinct from the recited HIF2 α .

(G.) Prior to the present disclosure, HIF was known to be regulated by oxygen via non-PAS mediated mechanisms only, which teaches away from any expectation that the HIF PAS domains would be sensory.

(H.) The HIF2 α PAS B shows a well-folded domain lacking the dynamic regions of PASK PAS A (Amezcua et al, 2002; pg 1352, col 1, lines 10-12) or the long insertion loops of NPAS2 PAS A (Erbel et al, 2003). Thus, HIF2 α PAS B would not be expected to bind ligand within its hydrophobic core.

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(I.) The declaration by Dr. Stephen Sprang confirms that the skilled artisan would not have expected HIF2 α PAS to provide a core for sensory ligand binding.

(J.) It is the PASK PAS A domain's unusual flexibility near the ligand binding sites that led Amezcua et al to hypothesize that said PAS domain might be able to bind small organic molecules, despite its well-packed core. This unusual flexibility near the ligand binding sites is not present in the HIF2 α PAS B domain.

(K.) Because of their structural and functional distinctness, one of skill would not deduce a function for the HIF2 α PAS B domain based on the function of the PASK PAS A domain.

These arguments are not found or found to be persuasive for the following reasons.

(F) Reply: This assertion is not found to be persuasive. It was known in the art that both HIF1 α and HIF2 α are heterodimeric, oxygen-sensitive transcription factors. Ema et al, 1997 teach that the basic residues of the bHLH regions of HIF1 α and HIF2 α are completely conserved and that both HIF1 α and HIF2 α interact with Arnt (pg 4274, para 13; Table 1). Moreover, Ema et al demonstrate that both HIF1 α and HIF2 α bind and activate the Epo HRE sequence in response to hypoxia (Fig 3). Therefore, HIF1 α and HIF2 α have similar structures and are likely to have overlapping, if not identical, functions.

(G) Reply: It is acknowledged that the art teaches that non-PAS domain mediated mechanisms can regulate the response of HIF to oxygen. However, said teachings do not provide a *prima facie* case against the PAS domain modulating an effect of oxygen or mediating the effect of other ligands on HIF. PAS domains were known to be sensory (Taylor et al, 1999; Cusanovich et al, 2003; esp pg 4765-4769). Also, see (J) below.

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(H) Reply: It is acknowledged that Amezcua et al state that a reason they predicted that the PASK PAS A domain binds organic compounds is that said domain is flexible in the region analogous to the ligand binding sites for other PAS domains. The fact that the PASK PAS A domain is flexible in said region does not provide a *prima facie* case against the HIF2 α PAS B domain binding ligands within its core. Moreover, Amezcua et al also state, as the first reason they predicted that the PASK PAS A domain binds organic compounds, that organic compounds play a key role in PAS domain signaling processes (pg 1352, parag 1).

As stated in the prior action, any teachings of Erbel et al are not relevant to the instant rejection, since Erbel et al was published after the filing date.

(I) Reply: The declaration by Dr. Stephen Sprang is acknowledged. Therein a summary of the state of the art at the time of filing is first provided. Dr. Sprang asserts that the HIF2 α PAS B domain presents a well-folded domain, in contrast with the dynamic regions of PASK PAS A, which removes any expectation of core ligand binding. The declaration further asserts that the structure of the ligand-free HIF2 α PAS B domain contrast with the many pre-bound small ligand-binding domains, which have either a pre-formed cavity or adopt an unfolded conformation; the HIF2 α PAS B domain structure shows neither of these. Dr. Sprang provides his opinion that, at the time of filing, the skilled artisan would not have expected the HIF2 α PAS B domain to provide a core for sensory ligand binding.

These assertions are not found to be persuasive. As explained in (H) above, the fact that the PASK PAS A domain is flexible does not provide a *prima facie* case against the HIF2 α PAS B domain binding ligands within its core. It is acknowledged that some pre-bound PAS domains have either a pre-formed cavity or adopt an unfolded conformation. However, again, structural

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characteristics of other PAS domains do not, alone, provide a *prima facie* case against ligands binding to the HIF2 α PAS B domain. Moreover, Amezcua et al teach that some PAS domains, containing well-packed hydrophobic cores, lacking any obvious cavities for binding of small ligands and folding stably in a ligand-free state, are not precluded from functioning as sensors (pg 1358, para 4). Amezcua et al further state that: "a very broad range of PAS domains, including those that do not copurify with ligands when isolated from natural sources, may serve sensor roles in vivo" (pg 1358, para 5). Therefore, Amezcua et al clearly suggest that PAS domains having a tightly packed core, such as the HIF2 α PAS-B domain, may still bind small molecules within their core and act as sensors.

(J) Reply: It is acknowledged that binding of ligand to the PASK PAS A domain is mediated by a flexible region. However, as stated above, characteristics of PASK PAS A domain binding do not provide a *prima facie* case that the HIF2 α PAS B domain cannot bind a ligand within its core. Moreover, it was accepted at the time of filing that PAS domains are signaling modules that monitor changes in environmental conditions via core-bound molecules (Taylor et al, 1999; pg 480, para 1; pg 488, para 3; pg 490, para 2). Furthermore, Cusanovich et al clearly teach that PAS domains have a common signaling mechanism, whereby a ligand bound in the central core alters associated hydrophobic residues leading to an alteration in the surface binding characteristics of the domain (pg 4764). Thus, both Taylor et al and Cusanovich et al teach that, more likely than not, any PAS domain will bind a ligand in its core.

(K) Reply: The Office is not deducing a function for the HIF2 α PAS B domain based on the function of the PASK PAS A domain. The prior action merely uses the PASK PAS A

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domain as an example for a PAS domain that has a well-packed hydrophobic core but still binds ligand within said core.

For these reasons and those presented in the prior actions, rejection of Claim 21 under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995 is maintained.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants'

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remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
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SHERIDAN SWOPE, PH.D.
PRIMARY EXAMINER